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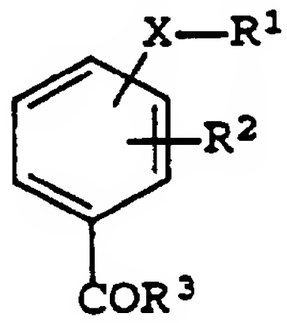

(1)

(57) Abstract

The present invention relates to methods of stimulating collagen synthesis and of smoothing or removing wrinkles, which comprise administering an effective amount of a benzoic acid derivative of formula (1) or a salt thereof, wherein X is -O- or -N(R^4)- (R^4 is H or the like), R^1 is a C_{4-25}-alkyl or C_{4-25}-alkenyl group, R^2 is H, OH, or a C_{1-6}-alkoxyl or C_{1-6}-alkanoyloxy group, and R^3 is -OR^5 or -N(R^6)R^7 (R^5 is H, or a C_{1-25}-alkyl or C_{1-25}-alkenyl group), and R^6 and R^7 are individually H, or a C_{1-3}-alkyl or C_{1-3}-alkenyl group, and use of this compound for agents for stimulating synthesis of collagen, and smoothing or removing wrinkles. This compound (1) stimulates collagen synthesis in human dermal fibroblasts and consequently smooths or removes wrinkles caused by aging and/or photoaging.

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DESCRIPTION

TITLE OF THE INVENTION

METHOD OF SMOOTHING OR REMOVING WRINKLES AND METHOD OF STIMULATING COLLAGEN SYNTHESIS

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to methods of smoothing or removing wrinkles and of stimulating collagen synthesis using benzoic acid derivatives, and use of the benzoic acid derivatives for an agent for smoothing or removing wrinkles (hereinafter referred to as "wrinkle-smoothing agent") and an agent for stimulating collagen synthesis.

Discussion of the Background:

The skin consists of epidermis, dermis and subcutaneous tissue. Of these, the dermis plays an important role as a connective tissue in support of the skin, maintenance of homeostasis and the like. In the dermis, fibroblasts produce fibrous proteins such as collagen, elastin and fibronectin and glycosaminoglycans such as hyaluronic acid. These compounds form a three-dimensional structure which maintains the elasticity of the connective tissue.

The skin undergoes aging and photoaging in response to chronic ultraviolet irradiation. First, the dermal thickness decreases and atrophies. Second, skin elasticity is decreased, which finally leads to formation of wrinkles and saggings, which are the most characteristic changes found on aged skin (Marks R., Biochemistry and Physiology of the Skin, Oxford Univ. Press, 1983).

When these phenomena are biochemically observed, the aging of the dermis is biochemically linked to the amount of collagen in the skin. Collagen is a major component of connective tissue. The amount of collagen in the skin decreases by 35% from 20 years to 80 years of age, resulting in an overall decrease of dermal thickness (Shuster S., British Journal of Dermatology, 93, 639 (1975)). This decrease is a result of (1) declining collagen metabolism with age and (2) increasing amounts of disordered intermolecular

crosslinking (A.M. Kligman, "Aging and Skin", p. 221 (1986)), glycosylation and the like in collagen fibers. Not only do these changes lead to an overall decrease in the amount of collagen, but they also lead to an increase in the amount of insoluble collagen (Legraed Y., Pathological Biology, 17, 991 (1969)). These cumulative changes result in connective tissue hardening and loss of flexibility and expansibility, eventually leading to the formation of wrinkles and the like in the skin.

To combat the loss of collagen, cosmetic compositions containing collagen have been marketed with a view to supplying the skin with collagen. However, collagen applied to the skin does not sufficiently penetrate into the dermis. Therefore, such cosmetic compositions fail to smooth or remove wrinkles. If collagen synthesis in dermal fibroblasts can be stimulated, it is expected that the skin would be supplemented with newly synthesized collagen. Moreover, it is expected that the metabolic turnover of collagen would also be activated, thereby increasing the amount of newly synthesized soluble collagen. As a result, the flexibility and expansibility of the connective tissue would be improved, and so the morphological changes of the cutaneous aging typified by wrinkles would be halted, if not improved.

Retinoic acid has attracted attention as a wrinkle-smoothing agent. Application of retinoic acid to the skin correlates with an increase in skin smoothness or removal of wrinkles and stimulation of collagen synthesis in the dermis (E. Schwartz et al, J. Invest. Dermatol., 96, 975 (1991); F. Bryce et al, Photodermatol., 190, 352 (1990); and R. Marks et al, Br. J. Dermatol., 122, 91 (1990)). However, retinoic acid application can lead to such side effects as irritation, erythema, pachymenia and teratogenesis. Therefore, it cannot be added into general drugs, quasi-drugs, cosmetic compositions and the like.

Vitamin C and derivatives thereof, 1α,25-dihydroxyvitamin D_3, extract of ginseng, milk sera of mammals have all been used as agents for stimulating collagen synthesis (J. Dobak et al,

J. Dermatol. Sci., 8, 18 (1984); and Japanese Patent Application Laid-Open Nos. 29080/1990 and 20206/1991), and the like. However, these agents are not yet fully satisfactory in points of percutaneous absorption, stability, effects and the like.

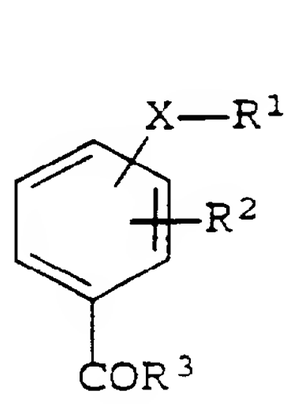
SUMMARY OF THE PRESENT INVENTION

It is, therefore, an object of the present invention to provide an agent for stimulating collagen synthesis and a wrinkle-smoothing agent, which are good in percutaneous absorption, chemical stability and the like.

In view of the foregoing circumstances, the present inventors have conducted screening of various compounds as to effects of stimulating collagen synthesis and of smoothing or removing wrinkles. As a result, they found that a benzoic acid derivative of the formula (1), which will be described subsequently, has excellent effects of stimulating collagen synthesis and of smoothing or removing wrinkles.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a method of smoothing or removing wrinkles, which comprises administering an effective amount of a benzoic acid derivative of the formula (1) or a salt thereof:



(1)

wherein

X is -O- or -N(R^4)-; in which R^4 is a hydrogen atom, C_{1-11}-alkyl, C_{2-11}-alkenyl, C_{1-11}-alkanoyl or C_{1-11}-alkoxycarbonyl group;

R^1 is a C_{4-25}-alkyl or a C_{4-25}-alkenyl group, which can be substituted with a hydroxyl group and which can contain a

heteroatom in a carbon chain or which can be substituted with a heteroatom;

R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl group or a C_{1-6}-alkanoyloxy group; and

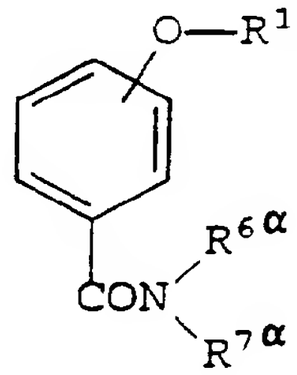
R^3 represents $-OR^5$ or $-N(R^6)R^7$, in which R^5 is a hydrogen atom or C_{1-25}-alkyl or C_{2-25}-alkenyl group, which can contain a heteroatom in the carbon chain or which can be substituted with a heteroatom, and R^6 and R^7 are, independently, a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

The present invention also provides a method of stimulating collagen synthesis in the skin, which comprises administering an effective amount of the benzoic acid derivative of the formula (1) or the salt thereof.

The present invention further provides a use of the benzoic acid derivative of the formula (1) or the salt thereof as a wrinkle-smoothing agent.

The present invention still further provides a use of the benzoic acid derivative of the formula (1) or the salt thereof as an agent for stimulating collagen synthesis in the skin.

The present invention provides novel benzoic acid amide derivatives of the formula (1α) or a salt thereof:



(1α)

wherein

$R^{1\alpha}$ is a C_{8-24}-hydroxyalkyl group or a 3,7,11-trimethyl-2,6,10-dodecatrienyl group; and

$R^{6\alpha}$ and $R^{7\alpha}$ are, independently, a hydrogen atom or a C_{1-3}-alkyl group, which can be substituted by a hydroxyl group.

The present invention also provides a use of the benzoic acid amide derivative of the formula (1α) or a salt thereof in an external skin care preparation.

The present invention further provides an external skin care composition comprising the benzoic acid amide derivative represented of the formula (1α) or the salt thereof.

Benzoic acid derivatives (1) useful in the practice of the present invention have heretofore been known, for example, as insecticides and synthetic intermediates thereof (USP 3,718,618, USP 4,051,319, DE 2144936, DE 2021227, etc.), depressants of sebum secretion (Japanese Patent Application Laid-Open Nos. 153616/1989 and 153617/1989), seborrhea-inhibiting cosmetics (Japanese Patent Application Laid-Open Nos. 165313/1986 and 165352/1986 and DE 4033562), insect juvenile hormones (Fiziol. Art. Veshchestva, 1, 27 (1977) and USP 3,847,907), and the like. However, their effects on collagen synthesis and smoothing or removing wrinkles have not been known at all.

Suitable heteroatoms which can be in a carbon chain include -O-, -S-, -S(O)-, $-S(O)_2-$, -NH- and the like. Suitable heteroatoms which can be substituents include =O, -OH, =S, -SH, $-SO_2^-$, $-SO_3$, $-NH_2$, and the like.

Suitable halogen atoms include fluorine, chlorine, bromine and iodine.

R^1 is a C_{4-25}-alkyl or a C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group, and which can be linear, branched or cyclic.

Preferred unsubstituted, linear C_{4-25}-alkyl groups include n-butyl, n-pentyl, n-hexyl, n-octyl, n-decyl, n-dodecyl, n-tetradecyl and n-hexadecyl groups. Preferred unsubstituted, branched C_{4-25}-alkyl groups include isobutyl, sec-butyl, t-butyl, 4-methylpentyl, 5-methylhexyl, 2,4-dimethylpentyl, 3,5-dimethylhexyl, 6-methylheptyl, 4,6-dimethylheptyl, 2,4,6-trimethylheptyl, 2-ethylhexyl, 7-methyloctyl, 11-methyldodecyl, 3,7-dimethyloctyl, 3,5,5-trimethylhexyl and 3,7,11-trimethyldodecyl groups. Preferred unsubstituted, cyclic C_{4-25}-alkyl groups include cyclopentyl, cyclohexyl, cyclohexylmethyl and cyclohexylethyl groups.

Preferred unsubstituted, linear C_{4-25}-alkenyl groups include 4-pentenyl, 5-hexenyl, 7-octenyl, 9-decenyl and 11-

dodecenyl groups. Preferred unsubstituted, branched C_{4-25}-alkenyl groups include 4-methyl-2-pentenyl, 5-methyl-2-hexenyl, 6-methyl-2-heptenyl, 3,7-dimethyl-2-octenyl, 3,7,11-trimethyl-2-dodecenyl, 3,7-dimethyl-2,6-octadienyl and 3,7,11-trimethyl-2,6,10-dodecatrienyl groups. Preferred unsubstituted, cyclic C_{4-25}-alkenyl groups include 1-cyclopentenyl and 1-cyclohexenyl groups and groups derived from vitamins, such as a retinyl group.

Preferred linear, branched or cyclic C_{4-25}-alkyl or C_{4-25}-alkenyl groups substituted by a hydroxyl group include 8-hydroxyoctyl, 10-hydroxydecyl, 11-hydroxyundecyl, 12-hydroxydodecyl and 12-hydroxyoctadecyl groups. Preferred C_{4-25}-alkyl or C_{4-25}-alkenyl group which contain a heteroatom in a carbon chain or which are substituted with a heteroatom include groups derived from vitamins such as vitamin E and vitamin C, such as tocopheryl and ascorbyl groups.

R^2 is a C_{1-6}-alkoxyl group or C_{1-6}-alkanoyloxy group, which can be linear or branched. Preferred C_{1-6}-alkoxyl groups include methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and n-pentyloxy groups. Preferred C_{1-6}-alkanoyloxy groups include formyloxy, acetyloxy, propanoyloxy, butanoyloxy and hexanoyloxy groups.

R^4 is a C_{1-11}-alkyl, C_{2-11}-alkenyl, C_{1-11}-alkanoyl or C_{1-11}-alkoxycarbonyl group, which can be linear or branched. Preferred C_{1-11}-alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-octyl and 3,7-dimethyloctyl groups. Preferred C_{2-11}-alkenyl groups include allyl, butenyl and 3,7-dimethyl-2,6-octadienyl groups. Preferred C_{1-11}-alkanoyl groups include acetyl, propanoyl and octanoyl groups. Preferred C_{1-11}-alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl and octyloxycarbonyl groups.

R^5 is a C_{1-25}-alkyl or C_{2-25}-alkenyl group, preferably a C_{1-15}-alkyl or C_{2-15}-alkenyl group, which can contain a heteroatom in a carbon chain or which can be substituted with a heteroatom and which can be linear, branched or cyclic. Preferred linear C_{1-25}-alkyl group include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-octyl, n-decyl, n-

dodecyl, n-tetradecyl and n-hexadecyl groups. Preferred branched C_{1-25}-alkyl groups include isopropyl, isobutyl, sec-butyl, t-butyl, 4-methylpentyl, 5-methylhexyl, 2,4-dimethylpentyl, 3,5-dimethyl hexyl, 6-methylheptyl, 4,6-dimethylheptyl, 2,4,6-trimethylheptyl, 2-ethylhexyl, 7-methyloctyl, 11-methyldodecyl, 3,7-dimethyloctyl and 3,7,11-trimethyldodecyl groups. Preferred cyclic C_{1-25}-alkyl groups include cyclopentyl and cyclohexyl groups.

Preferred linear C_{2-25}-alkenyl groups include vinyl, allyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 7-octenyl, 9-decenyl and 11-dodecenyl groups. Preferred branched C_{2-25}-alkenyl groups include 4-methyl-2-pentenyl, 5-methyl-2-hexenyl, 6-methyl-2-heptenyl, 3,7-dimethyl-2-octenyl, 3,7,11-trimethyl-2-dodecenyl, 3,7-dimethyl-2,6-octadienyl and 3,7,11-trimethyl-2,6,10-dodecatrienyl groups. Preferred cyclic C_{2-25}-alkenyl groups include 1-cyclopentenyl and 1-cyclohexenyl groups, and groups derived from vitamins, such as a retinyl group.

Preferred C_{1-25}-alkyl or C_{2-25}-alkenyl group which contain a heteroatom in a carbon chain or which are substituted with a heteroatom groups derived from vitamins such as vitamin E and vitamin C, such as tocopheryl and ascorbyl groups.

R^6 and R^7 are, independently C_{1-3}-alkyl or C_{2-3}-alkenyl groups, which can be substituted by a hydroxyl group. Preferably R^6 and R^7 are, independently, methyl, ethyl, n-propyl, isopropyl, 2-hydroxyethyl, 3-hydroxypropyl, vinyl and allyl groups. Most preferably, R^6 is a hydrogen atom and R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

In the general formula (1), particular preference is given to the case where:

X is -O- or -NH-;

R^1 is the C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group;

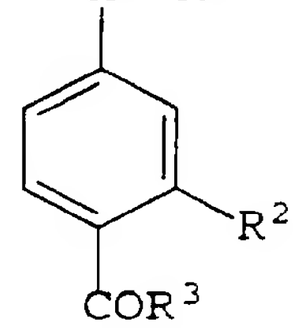
R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl or C_{1-6}-alkanoyloxy group;

R^5 is a hydrogen atom or a C_{1-25}-alkyl or C_{2-25}-alkenyl group;

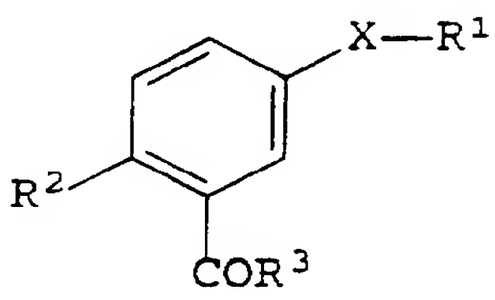
R^6 is a hydrogen atom; and

R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

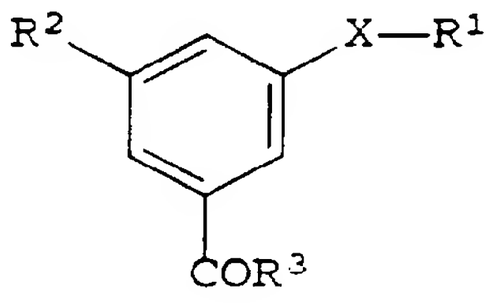
In the general formula (1), $-X-R^1$ and $-R^2$ can be substituted at any positions on the benzene ring. However, it is particularly preferred that they be substituted at positions indicated in the following formula (A), (B) or (C).



(A)



(B)



(C)

wherein R^1, R^2, R^3 and X have the same meaning as defined above.

No particular limitation is imposed on the salts of the benzoic acid derivatives (1) so far as they are pharmaceutically permissible salts. Examples thereof include salts of alkali metals such as sodium and potassium, salts of alkaline earth metals such as calcium and magnesium, ammonium salts, salts of mono-, di- or trialkanolamines, and salts of basic amino acids such as lysine and arginine. In the benzoic acid derivatives (1), stereoisomerism can be present in some cases. In the present invention, however, all stereoisomers and mixtures thereof can be used.

Specific preferable examples of the benzoic acid derivatives represented by the general formula (1) include:

methyl 4-(2-ethylhexyloxy)-2-hydroxybenzoate,
methyl 2-hydroxy-4-(3,5,5-trimethylhexyloxy)benzoate,
methyl 4-cyclohexylmethoxy-2-hydroxybenzoate,
methyl 4-(2-cyclohexylethoxy)-2-hydroxybenzoate,
methyl 4-(3,7-dimethyl-6-octenyloxy)-2-hydroxybenzoate,
ethyl 3-(2-ethylhexyloxy)-5-hydroxybenzoate,
methyl 5-(2-ethylhexyloxy)-2-hydroxybenzoate,
methyl 2-hydroxy-5-(3,5,5-trimethylhexyloxy)benzoate,
methyl 5-(2-cyclohexylethoxy)-2-hydroxybenzoate,
methyl 4-n-hexyloxy-2-hydroxybenzoate,
methyl 2-hydroxy-4-n-octyloxybenzoate,
methyl 4-n-decyloxy-2-hydroxybenzoate,
methyl 5-n-hexyloxy-2-hydroxybenzoate,
4-(2-ethylhexyloxy)-2-hydroxybenzoic acid,
2-hydroxy-4-(3,5,5-trimethylhexyloxy)benzoic acid,
4-cyclohexylmethoxy-2-hydroxybenzoic acid,
4-(2-cyclohexylethoxy)-2-hydroxybenzoic acid,
4-(3,7-dimethyl-6-octenyloxy)-2-hydroxybenzoic acid,
3-(2-ethylhexyloxy)-5-hydroxybenzoic acid,
5-(2-ethylhexyloxy)2-hydroxybenzoic acid,
2-hydroxy-5-(3,5,5-trimethylhexyloxy)benzoic acid,
5-(2-cyclohexyl-ethoxy)2-hydroxybenzoic acid,
4-n-hexyloxy-2-hydroxybenzoic acid,
5-n-hexyloxy-2-hydroxybenzoic acid,
2-hydroxy-4-n-octyloxybenzoic acid,

4-n-decyloxy-2-hydroxybenzoic acid,
N-(2-hydroxyethyl)-4-(2-ethylhexyloxy)-2-hydroxybenzamide,
N-ethyl-4-(2-ethylhexyloxy)-2-hydroxybenzamide,
2-acetoxy-4-cyclohexylmethoxybenzoic acid,
sodium 4-(2-ethylhexyloxy)-2-hydroxybenzoate,
methyl 4-((2E)-3,7-dimethyl-2,6-octadienyl-oxy)-2-hydroxybenzoate,
ethyl 4-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoate,
ethyl 5-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoate,
ethyl 3-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoate,
ethyl 3-((2E)-3,7-dimethyl-2,6-octadienyloxy)-5-hydroxy-benzoate,
ethyl 4-((2E)-3,7-dimethyl-2,6-octadienyloxy)-3-methoxybenzoate,
(2E)-3,7-dimethyl-2,6-octadienyl 4-((2E)3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoate,
4-((2E)3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoic acid,
5-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoic acid,
3-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzoic acid,
3-((2E)-3,7-dimethyl-2,6-octadienyloxy)-5-hydroxybenzoic acid,
2-hydroxy-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzoic acid,
4-((2E)-3,7-dimethyl-2,6-octadienyloxy)-3-methoxybenzoic acid,
2-acetoxy-4-((2E)-3,7-dimethyl-2,6-octadienyloxy)benzoic acid,
N-(2-hydroxyethyl)4-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-hydroxybenzamide,
4-((2E)-3,7-dimethyl-2,6-octadienyl)amino-2-hydroxybenzoic acid,
4-(((2E)-3,7-dimethyl-2,6-octadienyl)aminobenzoic acid,
3-(((2E)-3,7-dimethyl-2,6-octadienyl)aminobenzoic acid,
4-(((2E,6E)-3,7,11-trimethyl-
2,6,10-dodecatrienyl)amino)benzoic acid,
4-(((2E,6E)-3,7,11-trimethyl-2,6,10-octatrienyl)amino)benzoic acid,

3-(((2E,6E)-3,7,11-trimethyl-2,6,10-octatrienyl)amino)benzoic acid,
4-(2-ethylhexylamino)benzoic acid,
3-(2-ethylhexylamino)benzoic acid,
4-(3,5,5-trimethylhexyl amino)benzoic acid,
3-(3,5,5-trimethylhexylamino)benzoic acid,
4-N,N-bis((2E)-3,7-dimethyl-2,6-octadienyl amino)benzoic acid,
4-(N-methoxycarbonyl-N-((2E)-3,7-dimethyl-2,6-octadienyl)amino)benzoic acid,
4-(N-acetyl-N-((2E)-3,7-dimethyl-2,6-octadienyl)amino)benzoic acid,
4-(3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenyl)amino)benzoic acid,
3-(2-ethylhexyloxy)benzoic acid,
4-(2-ethylhexyloxy)benzoic acid,
3-(3,5,5-trimethylhexyloxy)benzoic acid,
4-(3,5,5-trimethylhexyloxy)benzoic acid,
3-dodecyloxybenzoic acid,
3-(12-hydroxydodecyloxy)benzoic acid,
4-dodecyloxybenzoic acid,
4-(12-hydroxydodecyloxy)benzoic acid,
3-(12-hydroxyoctadecyloxy)benzoic acid,
4-(12-hydroxyoctadecyloxy)benzoic acid,
3-(11-hydroxyundecyloxy)benzoic acid,
4-(11-hydroxyundecyloxy)benzoic acid,
3-((2E)-3,7-dimethyl-2,6-octadienyloxy)benzoic acid,
3-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzoic acid,
4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzoic acid,
4-(3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenyloxy)benzoic acid,
4-(3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-2H-1-benzopyran-6-oxy)benzoic acid,
4-((2E,6E)3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide,
4-((2E)3,7-dimethyl-2,6-octadienyloxy)benzamide,
4-(2-methyl-2-butenyloxy)benzamide,

4-(2-ethylhexyloxy)benzamide,
4-dodecyloxybenzamide,
4-(12-hydroxydodecyloxy)benzamide,
4-(12-hydroxyoctadecyloxy)benzamide,
4-(11-hydroxyundecyloxy)benzamide,
4-(10-hydroxydecyloxy)benzamide,
4-isostearyloxybenzamide,
N-(2-hydroxyethyl)-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide,
N,N-dimethyl-4-((2E,6E)3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide,
4-(N,N-bis-((2E)-3,7-dimethyl-2,6-octadienyl)amino)benzamide,
4-(N-methoxycarbonyl-N-((2E)-3,7-dimethyl-2,6-octadienyl)amino)benzamide,
4-(N-acetyl-N-((2E)-3,7-dimethyl-2,6-octadienyl)amino)-benzamide,
N-(2-hydroxyethyl)-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)-2-hydroxybenzamide, and
N,N-diethyl-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)-2-hydroxybenzamide.

In the general formula (1α), examples of the C_{8-24}-hydroxyalkyl group represented by $R^{1\alpha}$ includes linear, branched and cyclic hydroxyalkyl groups. Specific examples of the C_{8-24}-hydroxyalkyl group include 8-hydroxyoctyl, 10-hydroxydecyl, 11-hydroxyundecyl, 12-hydroxydodecyl and 12-hydroxyoctadecyl groups.

Examples of the C_{1-3}-alkyl groups, which can be substituted by a hydroxyl group, represented by $R^{6\alpha}$ and $R^{7\alpha}$ include methyl, ethyl, n-propyl, isopropyl, 2-hydroxyethyl and 3-hydroxypropyl groups.

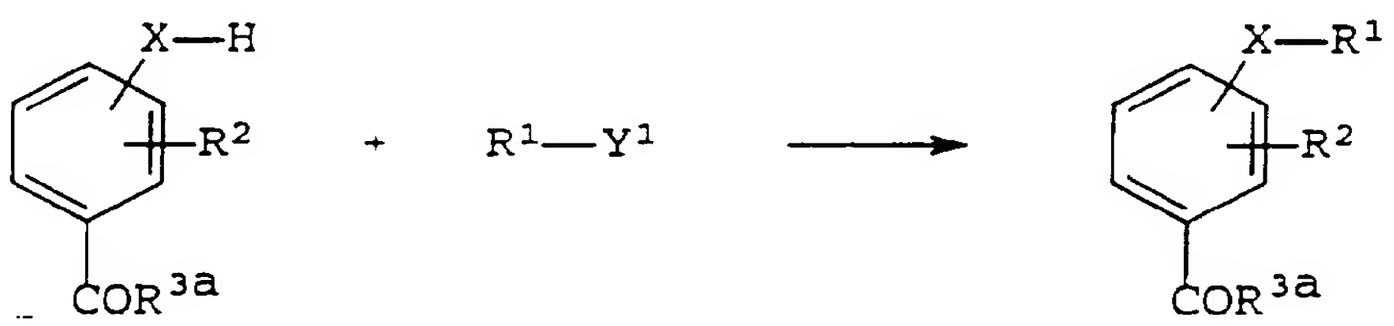
In the general formula (1α), the group represented by $-O-R^{1\alpha}$ can be substituted at any position of 2-, 3- and 4-positions on the benzene ring. However, it is preferably substituted at a 2- or 4-position, with the 4-position being particularly preferred.

Specific preferable examples of the benzoic acid amide derivatives represented by the general formula (1α) include

4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide,
4-(12-hydroxydodecyloxy)benzamide,
4-(12-hydroxyoctadecyloxy)benzamide,
4-(11-hydroxyundecyloxy)benzamide,
4-(10-hydroxydecyloxy)benzamide,
N-(2-hydroxyethyl)-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide, and
N,N-dimethyl-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide.

The benzoic acid derivatives (1) or the salts thereof are prepared, for example, in accordance with the following reaction schemes 1 to 4.

Reaction Scheme 1: (a case where R^3 in the formula (1) is the group other than a hydroxyl group)



(2) (3) (1a)

wherein, R^{3a} is a group other than a hydroxyl group represented by R^3,

Y^1 is a leaving group such as a halogen atom, or a p-toluenesulfonyloxy or methanesulfonyloxy group, and

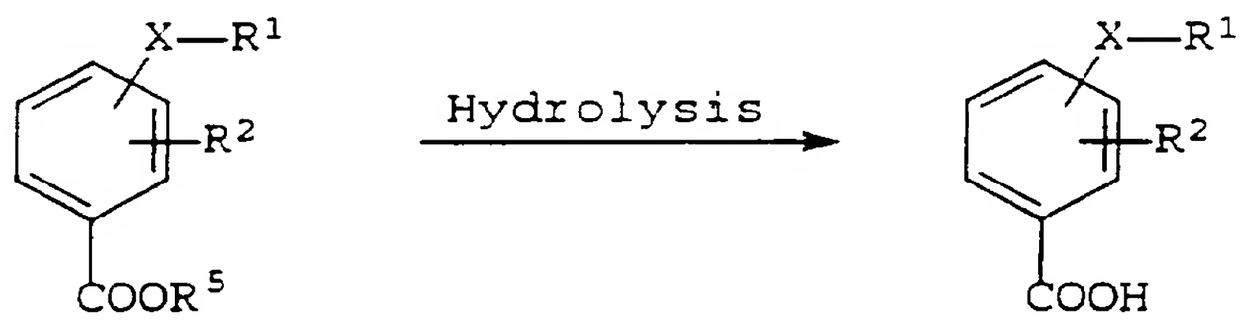
R^1, R^2 and X have the same meaning as defined above.

A compound (3) is reacted with a compound (2), thereby preparing a benzoic acid derivative (1a). This reaction is preferably carried out by using 0.5-3.0 moles of the compound (3) per mole of the compound (2) and stirring the resultant mixture at a temperature of generally 1 to 150°C, preferably 20 to 100°C for several hours. This reaction is preferably performed in the presence of a base. Any base can be used as the base so far as it adversely affects the reaction.

Preferred bases include sodium hydride, potassium carbonate, sodium hydroxide, potassium hydroxide and sodium carbonate.

Any solvent can be used as a solvent used in the above reaction so far as it is inert to the reaction. Preferred solvents include N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, ethanol, methanol and acetone. After completion of the reaction, the solvent is distilled off, and the residue is purified by any suitable means such as chromatography or recrystallization, whereby the benzoic acid derivative (1a) can be isolated.

Reaction Scheme 2:



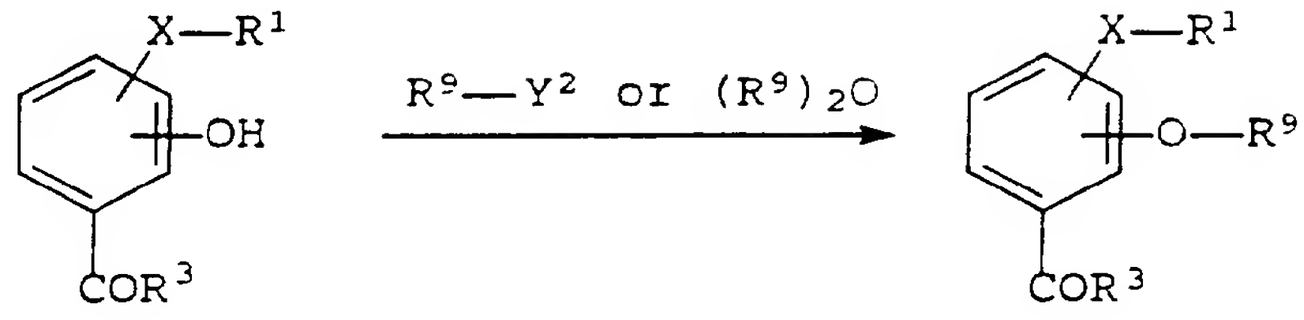
(1b) (1c)

wherein R^1, R^2, R^5 and X have the same meaning as defined above.

Namely, a compound (1b) is hydrolyzed, thereby preparing a compound (1c). This reaction is preferably carried out by using 1.03.0 moles of a base such as sodium hydroxide or potassium hydroxide per mole of the compound (1b) and stirring the resultant mixture at 20 to 100°C for several hours.

Any solvent can be used as a solvent used in the above reaction so far as it is inert to the reaction. Preferred solvents include N,N-dimethylformamide, dimethyl sulfoxide, ethanol, methanol, water, or mixtures thereof. After completion of the reaction, purification is conducted by any suitable means such as recrystallization or chromatography, whereby the compound (1c) is isolated.

Reaction Scheme 3:



(1d) (1e)

wherein R^9 means an C_{1-6}-alkanoyl group,

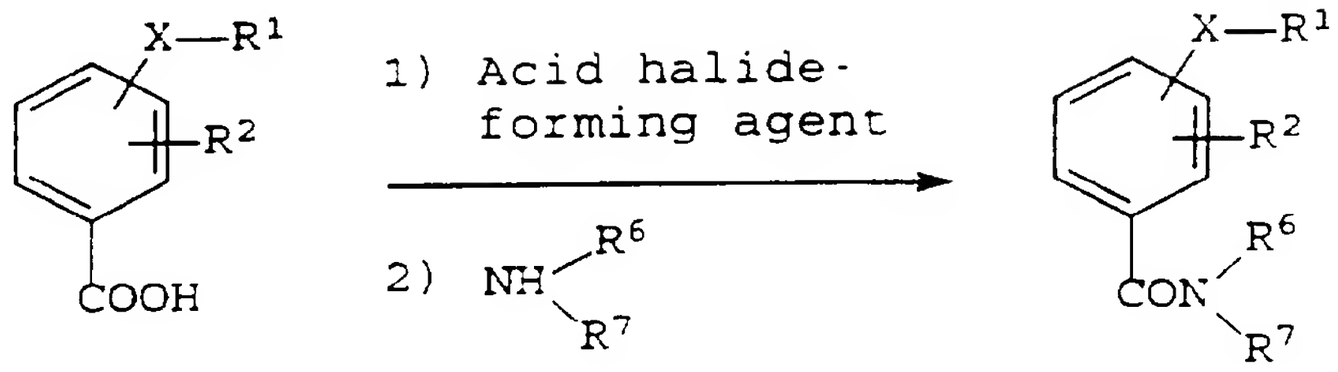
Y^2 is a halogen atom, and

R^1, R^3 and X have the same meaning as defined above.

Namely, an acid anhydride or acid halide is reacted with a compound (1d) in the presence of a base, whereby a benzoic acid derivative (1e), which is an O-acylated product, can be prepared. In this reaction, any base can be used as the base so far as it adversely affects the reaction. Pyridine or triethylamine is preferred.

This reaction is preferably carried out by using 1.0-3.0 moles of the acid anhydride or acid halide per mole of the compound (1d) and stirring the resultant mixture at a temperature of generally 0 to 150°C, preferably 20 to 100°C for several hours. Any solvent can be used as a solvent used in this reaction so far as it is inert to the reaction. Preferred solvents include N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, ethanol, methanol and acetone. After completion of the reaction, the solvent is distilled off, and the residue is purified by a means such as chromatography or recrystallization, whereby the compound (1e) can be isolated.

Reaction Scheme 4:



(1c) (1f)

wherein R^1, R^2, R^6, R^7 and X have the same meaning as defined above.

Namely, a compound (1c) is treated with an acid halide-forming agent such as thionyl chloride, and the resultant acid halide is then reacted with an amine in the presence of a base, whereby a compound (1f) can be prepared. The reaction of the compound (1c) with the acid halide-forming agent is carried out, for example, by adding the acid halide-forming agent to the compound (1c) in a solvent such as tetrahydrofuran, diethyl ether, methylene chloride, N,N-dimethylformamide or dimethyl sulfoxide and stirring the resultant mixture at a temperature of 0 to 100°C. The reaction of the thus-obtained acid halide with the amine is carried out, for example, by stirring the reactants in the presence of a base such as sodium hydroxide, potassium hydroxide or sodium carbonate at a temperature of -20 to 100°C. The resultant benzoic acid derivatives (1) can be converted into salts in accordance with a method known *per se* in the art.

Since the thus-obtained benzoic acid derivatives (1) or the salts thereof have an effect of markedly stimulating collagen synthesis in human skin fibroblasts, and moreover possess an effect of smoothing or removing wrinkles, they can be used as agents for stimulating collagen synthesis and wrinkle-smoothing agents.

The agents for stimulating collagen synthesis according to the present invention can be administered in either way of external application and internal use. External application is preferred. The wrinkle-smoothing agents are preferably administered in a manner of external application. In the agents for stimulating collagen synthesis and the wrinkle-smoothing agents according to the present invention, external skin care compositions as one of their manner of use can contain a base for external application and other medicinally-effective agents, which are routinely used, in addition to the benzoic acid derivative or the salt thereof.

As the base for external application used herein, any of an oily base, an oil/water or water/oil emulsion-type base and water can be used. No particular limitation is imposed on the oily bases. For example, plant oils, animal oils, synthetic oils, fatty acids, natural and synthetic glycerides, etc. can be mentioned. No specific limitation is imposed on the medicinally-effective agents. It is also possible to contain moisturizers, ultraviolet adsorbents, alcohols, chelating agents, pH adjustors, antiseptics, thickeners, coloring matters, perfume bases, plants extracts and the like in combination as needed.

No particular limitation is imposed on the medicinally-effective ingredients. For example, one or more of analgesic and antiphlogistic agents, disinfectants, astringents, emollients, hormones, vitamins and the like can be used suitably as needed.

Examples of the preparation form of these external skin care compositions include ointments, creams, milk lotions, liquid lotions, packs and foundations.

No particular limitation is imposed on the proportion of the benzoic acid derivative (1) or the salt thereof in the external skin care composition. In the case of the emulsion-type external skin care composition, however, its proportion can preferably be 0.001-10 wt.% (hereinafter indicated.merely by "%"), particularly 0.001-5% of the total weight of the composition. In the case of the oil-based external skin care

composition containing a liquid hydrocarbon such as squalane as a base ingredient, its proportion can preferably be 0.001-20%, particularly 0.01-10% of the total weight of the composition.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLES

Synthesis Example 1:

A 100-ml flask equipped with a dropping funnel was charged with 2.00 g (14.6 mmol) of 4-hydroxy-benzamide, 2.42 g (17.5 mmol) of potassium carbonate and 15 ml of N,N-dimethylformamide. While stirring the contents at room temperature, 7.03 g (29.2 mmol) of farnesyl chloride were added dropwise over 10 minutes. After the addition, the resultant mixture was heated to 80°C and stirred for 3 hours. The mixture was poured into 300 ml of diluted hydrochloric acid, followed by extraction with ethyl acetate. The extract was washed with 100 ml of water and 200 ml of saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the resultant crude product was purified by chromatography on silica gel, thereby obtaining 3.09 g (yield: 62%) of 4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyl)benzamide. The results of its analysis are described below.

Form: Colorless solid.

Melting point: 76.5-77.7°C.

^{1}H-NMR ($CDCl_3$, ppm):

1.60-1.75(m,12H),

2.00-2.16(m,8H),

4.59(d,2H,J=6.5Hz),

4.98-5.22(m,2H),

5.48(t,1H,J=6.3Hz),

5.79(brs,2H),
6.94(d,2H,J=8.8Hz),
7.77(d,2H,J=8.8Hz).
IR (KBr, cm^{-1}):
3404, 3176, 2924, 1648, 1620, 1426, 1398, 1254.

Synthesis Example 2:

1-Bromododecane, 12-bromododecanol and 1-bromo-2-ethylhexane, were separately used in place of farnesyl chloride in Synthesis Example 1, thereby synthesizing 4-dodecyloxybenzamide, 4-(12-hydroxydodecyloxy)benzamide and 4-(2-ethylhexyloxy)benzamide, respectively.

4-Dodecyloxybenzamide:
Form: Colorless solid.
Melting point: 142.5-143.3°C.
^{1}H-NMR ($CDCl_3$, ppm):
0.88(t,3H,J=6.4Hz),
1.18-1.94(m,20H),
4.00(t,2H,J=6.5Hz),
5.83(brs,2H),
6.92(d,2H,J=8.8Hz),
7.76(d,2H,J=8.8Hz).
IR (KBr, cm^{-1}):
3420, 3192, 2928, 2856, 1648, 1616, 1424, 1396, 1256.

4-(12-Hydroxydodecyloxy)benzamide:
Form: Colorless solid.
Melting point: 141.4-142.1°C.
^{1}H-NMR (CD_3OD, ppm):
1.66-1.90(m,20H),
3.52(t,2H,J=6.5Hz),
4.02(t,2H,J=6.4Hz),
6.81(d,2H,J=8.9Hz),
7.82(d,2H,J=8.9Hz).
IR (KBr, cm^{-1}):
3436, 3316, 3204, 2924, 2856, 1648, 1620, 1424, 1400, 1256.

4-(2-Ethylhexyloxy)benzamide:
Form: Colorless solid.
Melting point: 98.3-99.4°C.
^{1}H-NMR ($CDCl_3$, ppm):
0.80-1.05(m,6H),
1.18-1.90(m,7H),
3.89(d,2H,J=5.7OHz),
5.81(brs,2H),
6.94(d,2H,J=8.7Hz),
7.77(d,2H,J=8.7Hz).

Test Example 1:

Effect of benzoic derivatives (1) on collagen synthesis in human dermal fibroblasts (Dulbecco's modified essential medium (hereinafter abbreviated as "DMEM")).

Fibroblasts were cultured to confluency in DMEM containing 5% FCS (fetal calf serum). The medium was replaced with DMEM containing 0.5% FCS, to which each test compound was added to give a concentration of 1 μM to 10 μM, thereby incubating the culture at 37°C for 24 hours. Thereafter, tritium labeled proline (^{3}H-proline) was added (5 μCi/ml of the medium) to further continue the incubation at 37°C, thereby incorporating 3H-proline into collagenous protein. After 24 hours, the medium was recovered to determine the amount of ^{3}H-labeled collagen after purification (D. F. Webster and W. Harvey, Analytical Biochem., 96, 220 (1979)). The results are shown in Table 1. As a result, it was revealed that the benzoic acid derivatives (1) markedly stimulate collagen synthesis in human dermal fibroblasts.

Table 1

Test compound	Concentration (μM)	Rate of Synthesis of collagen (%)
Control	-	100
Compound 1	10	145
Compound 2	10	128
Compound 3	1	138
Compound 4	10	175
Compound 5	10	158
Compound 6	10	172
Compound 7	10	186
Compound 8	10	129
Compound 9	10	185
Compound 10	10	138
Compound 11	10	141
Compound 12	10	163
Compound 13	10	160
Compound 14	10	123
Compound 15	10	142
Compound 16	10	158
Compound 17	10	112
Compound 18	10	144
Compound 19	10	148
Compound 20	10	129
Compound 21	10	180

Compound 1: 4-(3,7-dimethyl-6-octenyloxy)-2-hydroxy-benzoic acid

Compound 2: 4-{(2E)-3,7-dimethyl-2,6-octadienyloxy}-2-hydroxybenzoic acid

Compound 3: 2-hydroxy-4-{(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy}benzoic acid

Compound 4: 4-{(2E,6E)-3,7,11-trimethyl-2,6,10-dodeca-trienyloxy)benzamide

Compound 5: 4-dodecyloxybenzamide

Compound 6: 4-(12-hydroxydodecyloxy)benzamide

Compound 7: 4-{(2E)-3,7-dimethyl-2,6-octadienyloxy)benzoic acid

Compound 8: 4-{(2E)-3,7-dimethyl-2,6-octadienylamino}benzoic acid

Compound 9: 4-{(2E,6E)-3,7,11-trimethyl-2,6,10-dodeca-trienylamino}-2-hydroxybenzoic acid

Compound 10: methyl 4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienylamino)-2-hydroxybenzoate

Compound 11: 4-((2E)-3,7-dimethyl-2,6-octadienyloxy)-2-methoxybenzoic acid

Compound 12: N-(2-hydroxyethyl)-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)-2-hydroxybenzamide

Compound 13: N,N-diethyl-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)-2-hydroxybenzamide

Compound 14: N,N-diethyl-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide

Compound 15: N-(2-hydroxyethyl)-4-((2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyloxy)benzamide

Compound 16: 4-((9Z)-9-octadecenyloxy)benzamide

Compound 17: 4-(methylheptadecyloxy)benzamide

Compound 18: 4-(methylheptadecyloxy)benzoic acid

Compound 19: 2-hydroxy-4-(methylheptadecyloxy)benzoic acid

Compound 20: 2-hydroxy-5-(methylheptadecyloxy)benzoic acid

Compound 21: 4-(methylheptadecylamino)benzoic acid.

Test Example 2:

Effect of the benzoic acid derivatives (1) on wrinkles formed on hairless mice by UVB irradiation.

(a) Hairless mice (HR/ICR, 9 week age at the beginning of the experiment) were irradiated by UVB 3 times a week by using 6 Toshiba health light lamps, 20SE. The amount of energy was measured by means of a UV-Radiometer UVR-305/365D manufactured by TOKYO OPTICAL Co. The dose upon one irradiation was determined to be 1 MED or less, i.e., 65 mJ in an amount of energy of 0.28 mW/cm^2. The irradiation was continued for 20 weeks. After confirming the fact that the mice had got wrinkles at their backs, they were divided into groups each consisting of 8 mice. Ethanol solutions separately containing the benzoic acid derivatives (1) in a concentration of 0.005% were applied 5 times a week to their corresponding groups of mice for 6 weeks in a dose of 80 μl. As a control, ethanol alone was applied in a dose of 80 μl like the samples. After completion of the application, the degree of wrinkles was visually observed to rank the samples in accordance with the following standard (wrinkle index) (Table 2).

Wrinkle index

1: Wrinkles were completely removed;
2: Wrinkles were scarcely observed;
3: Wrinkles were somewhat observed;
4: Wrinkles were observed to a great extent.

(b) In order to further analyze the particulars of wrinkles, upon elapsed time of 0 week (at the time each test compound was applied) and 6 weeks after the test compound was applied, skin replicas of the size of 1 cm^2 in diameter were gathered from 3 portions of the back in each of the mice using a Hydrophilic Exaflex hydrophilic vinylsilicone impression material. Each of these replicas was held horizontally and illuminated at an angle of 30 degrees from the horizontal direction, thereby finding the proportion of shadows of the wrinkles as an area percent (%) by means of an image analyzer.

A rate of smoothing of wrinkles upon the elapsed time of 6 weeks after the application to that upon 0 week was then determined in accordance with the following equation.

$$\text{Smoothing rate} = \left[\left(\frac{\text{Area percent upon 0 week on each test compound} - \text{Area percent after 6 weeks on each test compound}}{\text{Area percent upon 0 week on each test compound}}\right) - \left(\frac{\text{Area percent upon 0 week on ethanol} - \text{Area percent after 6 weeks on ethanol}}{\text{Area percent upon 0 week on ethanol}}\right)\right] \times 100$$

The results are shown in Table 2. As a result, it was found that the wrinkles formed on the backs of the hairless mice can be removed by applying the benzoic acid derivatives (1) thereto.

Table 2

Test compound	Wrinkle index	Smoothing rate (%)
Control	3.75	0
Compound 1	3.25	27.5
Compound 2	3.1	14.2
Compound 3	3	18.9
Compound 4	2.375	63.4
Compound 5	2.875	38.8
Compound 6	2.5	56.8
Compound 7	3.25	12.3
Compound 8	2.5	52.5
Compound 9	3.1	16.0
Compound 10	2.875	42.1
Compound 11	2.875	61.2
Compound 12	3.25	21.7
Compound 13	2.375	67.3
Compound 14	2.75	44.1
Compound 15	2.75	51.3
Compound 16	2.50	50.7
Compound 17	3.125	30.3
Compound 18	3.0	31.2
Compound 19	2.875	39.6
Compound 20	2.875	35.2
Compound 21	2.75	43.8

Preparation Example 1:

		(wt.%)
(1)	Compound 1	0.01
(2)	Cholesterol	0.5
(3)	Cholesteryl isostearate	1.0
(4)	Polyether-modified silicone	1.5
(5)	Cyclic silicone	20.0
(6)	Methylphenylpolysiloxane	2.0
(7)	Methylpolysiloxane	2.0
(8)	Magnesium sulfate	0.5
(9)	55% Ethanol	5.0
(10)	Carboxymethylchithin (Chithin Liquid HV, product of Ichimaru Pharcos Co., Ltd.)	0.5
(11)	Purified water	Balance

Components (1)-(7) were heated to 80°C to melt them, and the components (8)-(11) were added to the melt. The resultant mixture was intimately mixed to prepare a W/O type cream.

Preparation Example 2:

		(wt.%)
(1)	Polyoxyethylene (10) hardened castor oil	1.0
(2)	Sorbitan monostearate	0.5
(3)	Sodium stearoylmethyltaurine	0.5
(4)	Cetostearyl alcohol	2.0
(5)	Stearic acid	1.8
(6)	Compound 2	0.1
(7)	Cholesterol	1.5
(8)	Cholesteryl isostearate	1.0
(9)	Neopentyl glycol dicaprate	8.0
(10)	Methylpolysiloxane	5.0
(11)	Glycerol	5.0
(12)	Purified water	Balance

Components (1)-(10) were heated to 80°C to melt them, and the components (11)-(12) were added to the melt. The resultant mixture was intimately mixed to prepare an O/W type cream.

Preparation Example 3:

		(wt.%)
(1)	Compound 3	0.2
(2)	Silicon-coated zinc oxide	7.0
(3)	2-Ethylhexyl p-methoxycinnamate	3.0
(4)	Cholesteryl isostearate	1.0
(5)	Polyether-modified silicone	2.0
(6)	Methylpolysiloxane	5.0
(7)	Cyclic silicone	15.0
(8)	Magnesium sulfate	1.0
(9)	Glycerol	5.0
(10)	Purified water	Balance

Components (1)-(7) were heated to 80°C to melt them, and the components (8)-(10) were added to the melt. The resultant mixture was intimately mixed to prepare a cream.

Preparation Example 4:

		(wt.%)
(1)	Compound 4	0.05
(2)	White petrolatum	Balance
(3)	Cholesteryl isostearate	3.0
(4)	Liquid paraffin	10.0
(5)	Glyceryl ether	1.0
(6)	Glycerol	10.0

Components (1)-(6) were heated to 80°C to melt them, and then cooled, thereby preparing an ointment.

Preparation Example 5:

		(wt.%)
(1)	Compound 5	1.0
(2)	Polyvinyl alcohol	15.0
(3)	Sodium carboxymethylcellulose	5.0
(4)	Propylene glycol	3.0
(5)	Ethanol	8.0
(6)	Purified water	67.5
(7)	Perfume base	0.5
(8)	Antiseptic, oxidizing agent	q.s.

Components (1)-(8) were heated to 70°C to melt them, and then cooled, thereby preparing a wrinkle-smoothing agent of the pack type.

Preparation Example 6:

		(wt.%)
(1)	1,3-Butylene glycol	8.0
(2)	Glycerol	4.0
(3)	Sodium hyaluronate	1.0
(4)	Ethanol	3.0
(5)	Polyoxyethylene polyoxypropylene decyl tetradecyl ether	0.3
(6)	Compound 6	0.05
(7)	Purified water	Balance
(8)	Antiseptic	q.s.
(7)	Perfume base	q.s.

Components (1)-(8) were stirred into a dispersion, and 60% of purified water was then added to the dispersion, thereby providing a mixture A. On the other hand, components (4), (5), (6), (8) and (9) were stirred into a solution, and the remaining purified water was then added to the solution, thereby providing a mixture B. The mixture B was added to the

mixture A while stirring the mixture A, and the resultant mixture was stirred to prepare a wrinkle-smoothing agent of the lotion type.

Preparation Example 7:

		(wt.%)
(1)	1,3-Butylene glycol	8.0
(2)	Glycerol	4.0
(3)	Xanthan gum	0.3
(4)	Sodium chondroitin sulfate	0.1
(5)	Sodium hyaluronate	0.05
(6)	Ethanol	3.0
(7)	Polyoxyethylene polyoxypropylene decyl tetradecyl ether	0.3
(8)	Compound 7	0.2
(9)	Purified water	Balance
(10)	Antiseptic	q.s.
(11)	Perfume base	q.s.

Components (1)-(5) were stirred into a dispersion, and 65% of purified water was then added to the dispersion, thereby providing a mixture A. On the other hand, components (6), (7), (8), (10) and (11) were stirred into a solution, and the remaining purified water was then added to the solution, thereby providing a mixture B. The mixture B was added to the mixture A while stirring the mixture A, and the resultant mixture was stirred to prepare a wrinkle-smoothing agent of the liquid lotion (beauty wash) type.

INDUSTRIAL APPLICABILITY

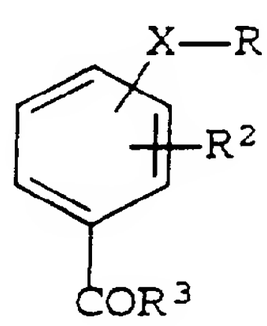
The benzoic acid derivatives (1) or the salts thereof stimulate collagen synthesis in human dermal fibroblasts and consequently smooth or remove wrinkles caused by aging and/or photoaging.

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

CALIMS

1. A method of smoothing or removing wrinkles, which comprises

administering an effective amount of a benzoic acid derivative of the formula (1) or a salt thereof:



(1)

wherein X is -O- or -N(R^4)-, in which R^4 is a hydrogen atom or a C_{1-11}-alkyl, C_{2-11}-alkenyl, C_{1-11}-alkanoyl or C_{1-11}-alkoxycarbonyl group,

R^1 is an C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group, which can contain a heteroatom in a carbon chain or which can be substituted with a heteroatom,

R^2 is a hydrogen atom, a hydroxyl group, an C_{1-6}-alkoxyl group or an C_{1-6}-alkanoyloxy group, and

R^3 is -OR^5 or -N(R^6)R^7, in which R^5 is a hydrogen atom or an C_{1-25}-alkyl or C_{2-25}-alkenyl group, which can contain a heteroatom in a carbon chain or which can be substituted with a heteroatom, and

R^6 and R^7 are, independently, a hydrogen atom or C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

2. The method according to Claim 1, wherein

X is -O- or -NH-,

R^1 is the C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group,

R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl group or a C_{1-6}-alkanoyloxy group,

R^5 is a hydrogen atom or a C_{1-25}-alkyl or C_{2-25}-alkenyl group,

R^6 is a hydrogen atom, and

R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

3. A method of stimulating collagen synthesis in the skin, which comprises administering an effective amount of the benzoic acid derivative or salt thereof according to Claim 1.

4. The method of stimulating collagen synthesis according to Claim 3, wherein

X is -O- or -NH-,

R^1 is the C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group,

R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl group or a C_{1-6}-alkanoyloxy group,

R^5 is a hydrogen atom or a C_{1-25}-alkyl or C_{2-25}-alkenyl group,

R^6 is a hydrogen atom, and

R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

5. Use of the benzoic acid derivative or the salt thereof according to Claim 1 for an agent for smoothing or removing wrinkles.

6. The use according to Claim 5, wherein

X is -O- or -NH-,

R^1 is the C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group,

R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl group or a C_{1-6}-alkanoyloxy group,

R^5 is a hydrogen atom or a C_{1-25}-alkyl or C_{2-25}-alkenyl group,

R^6 is a hydrogen atom, and

R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

7. Use of the benzoic acid derivative or salt thereof according to Claim 1 for an agent for stimulating collagen synthesis in the skin.

8. The use according to Claim 7, wherein

X is -O- or -NH-,

R^1 is the C_{4-25}-alkyl or C_{4-25}-alkenyl group, which can be substituted by a hydroxyl group,

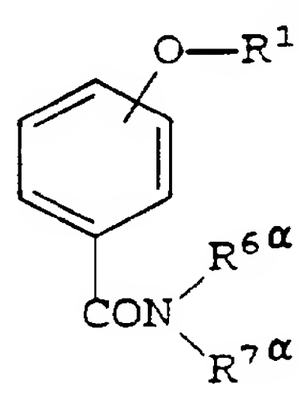
R^2 is a hydrogen atom, a hydroxyl group, a C_{1-6}-alkoxyl group or a C_{1-6}-alkanoyloxy group,

R^5 is a hydrogen atom or a C_{1-25}-alkyl or C_{2-25}-alkenyl group,

R^6 is a hydrogen atom, and

R^7 is a hydrogen atom or a C_{1-3}-alkyl or C_{2-3}-alkenyl group, which can be substituted by a hydroxyl group.

9. A benzoic acid amide derivative of the formula (1α) or a salt thereof:



(1α)

wherein $R^{1\alpha}$ is a C_{8-24}-hydroxyalkyl group or a 3,7,11-trimethyl-2,6,10-dodecatrienyl group, and

$R^{6\alpha}$ and $R^{7\alpha}$ are, independently, a hydrogen atom or a C_{1-3}-alkyl group, which can be substituted by a hydroxyl group.

10. Use of the benzoic acid amide derivative or salt thereof according to Claim 9 for an external skin care preparation.

11. An external skin care composition comprising the benzoic acid amide derivative or salt thereof according to Claim 9.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 95/02498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48 C07C235/46 C07C235/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 643 035 (KAO CORP) 15 March 1995 see claims; examples	1-8
X	& WO,A,94 21591	1-8
A	WO,A,94 09756 (UNILEVER PLC ;UNILEVER NV (NL)) 11 May 1994 see claims	1-11
A	EP,A,0 315 913 (HENKEL KGAA) 17 May 1989 see claims	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

tc. ›nal Application No
PCT/JP 95/02498

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